Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM

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December 21, 2005

Andrew C. von Eschenbach, M.D.
Acting Commissioner
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857-0001

Dear Dr. von Eschenbach:

This letter pertains to the Food and Drug Administration's investigation of the deaths of four American women who died from septic shock following the use of the abortifacient, Mifeprex® (mifepristone, also commonly known as "RU-486").

On or about July 19, 2005, members of Congress became aware that four American women had died after taking RU-486.[1] FDA and the Centers for Disease Control justifiably investigated these fatalities, and a summary of the results was published recently in the *New England Journal of Medicine*.[2] I am encouraged by the joint FDA-CDC effort to examine the serious health and public safety risks posed by RU-486. The available data strongly suggest that we have much more to learn. Consequently, I was pleased to learn that FDA intends to hold scientific meetings next year to examine these infection-related deaths.[3]

As FDA and CDC confirmed, each of the four women who died from septic shock were infected by *Clostridium sordellii*, a potent anaerobic bacteria. It is also known that a Canadian woman died from septic shock linked to *C. sordellii* after taking RU-486.[4] These women did not possess other risk factors or underlying medical conditions that would have predisposed them to sepsis. In general, they were young and healthy. Moreover, although these women complained of weakness, nausea and vomiting, these symptoms are consistent with the medical abortion

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[1] Prior to that date, members of Congress and the public were only aware of two deaths.

[2] Marc Fischer, M.D. *et al.*, *Fatal Toxic Shock Syndrome Associated with Clostridium sordellii after Medical Abortion*, 353 N. Engl. J. Med. 2352 (2005).

[3] Gardiner Harris, *Deaths After Abortion to Be Studied by Officials*, N.Y. Times, Nov. 23, 2005, available at http://www.nytimes.com/2005/11/23/national/23pill.html?ex=1133586000&en=2e0843655c6f7bf6&ei=5070 (last visited December 1, 2005).

[4] Christian Sinave, *et al.*, *Toxic Shock Syndrome Due to Clostridium sordellii: A Dramatic Postpartum and Postabortion Disease*, 35 Clinical Infectious Diseases 1441 (2002).

procedure, and they had no fever to indicate an infection. Nevertheless, each woman died soon after being hospitalized.

I am deeply concerned about the safety of the RU-486 regimen and the possibility that there may be some deaths and many non-fatal adverse events that have gone unreported. An article accompanying the *New England Journal of Medicine* Report, referenced above, notes that RU-486 abortions present patients with a ten times greater risk of death than surgical abortions done early in a pregnancy.[5] The *New England Journal of Medicine* Report investigating the sudden post-RU-486 deaths of healthy young women states the obvious: "These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion."[6]

Dr. von Eschenbach, it is imperative that the FDA continue to fully investigate the potential harm posed by RU-486. This must be done in order to reassure women, their families, and their doctors that women's health is the FDA's paramount consideration in allowing this drug to remain on the market. Safety concerns based on scientific analysis must be followed wherever they lead. To that end, and in light of the critical public health issues involved in this matter, I am requesting information and documents relating to FDA's investigation of these deaths in preparation for an oversight hearing.

Please submit your responses to each request below to my staff in writing as soon as you are able to answer that item. Additionally, in those instances in which actions have been taken by CDC in conjunction with FDA or FDA is aware of steps taken by CDC alone, please so indicate.[7]

I request the following documents regarding the four American women who died from septic shock following RU-486 abortions: (1) copies of all notes, physician charts and other records prepared by the treating healthcare providers (including emergency room records); (2) autopsy reports; (3) pathology and laboratory reports; (4) information on the dosage, timing, and route of administration of any medications given.

I have the following additional requests for information on related topics:

1. In August 2001, a Canadian woman died after taking RU-486 during a clinical trial.[8] Has FDA investigated this death?

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[5] Michael F. Greene, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, 353 N. Engl. J. Med. 2317, 2318 (2005). Dr. Greene has affirmed this ratio in comments to reporters: "Greene said that while the deaths are 'tragic,' the mifepristone-misoprostol regimen remains very safe. Surgical abortions performed at seven weeks of gestation or less carry an estimated risk of maternal mortality of about one in 1,000,000, he said. Risks for death by using Mifeprex-misoprostol are higher — about one in 100,000 — but still very low, he said." (E.J. Mundell, *Abortion Pill Deaths Probed*, ABC News, November 30, 2005. Available at http://www.abcnews.go.com/Health/Healthology/story?id=1360362 (last visited December 7, 2005).)

[6] Fischer, *op. cit.*, at 2352.

[7] In such instances, provide the names and contact information of all relevant CDC offices and personnel.

[8] Sinave, *op. cit.*

a. If so, please provide all of FDA's findings, memos, and reports on this adverse event.
b. In addition, provide the following documents if they are in your possession: (1) copies of all notes, physician charts and other records prepared by the treating healthcare providers (including emergency room records); (2) autopsy reports; (3) pathology and laboratory reports; (4) information on the dosage, timing, and route of administration of any medications given.
c. If the FDA has not investigated this death, please explain why not.

2. Has FDA investigated, examined, or inquired as to whether the British mifepristone-related abortion death in May-June 2002 was caused by septic shock?
   a. If so, please provide, in full detail, FDA's findings and documentation as requested in item #1, *supra* (Canadian death). (FDA ISR # 3928293-5; British case # 2002108411GB)
   b. If the FDA has not investigated, examined or inquired into this death, please explain why.

3. For each of the four Californians who died following administration of the RU-486 regimen, please examine those records and provide the following information, if available:
   a. What specimens were cultured, *i.e.*, blood, sputum, urine, vaginal, etc? Please provide the results of each culture.
   b. What information has been collected on other infections which may have been present but were not lethal?
   c. Please provide the complete blood counts in both the emergency room and the hospital.
   d. Please provide the kinds and amounts of intravenous fluids given, including packed red blood cells.
   e. Please provide the dates of all clinic or ER visits prior to hospitalization, and which actions were taken at each date.
   f. Please provide the vital signs on admission to both the ER and to the hospital.

4. Is FDA aware of cases, other than the four U.S. fatalities, in which reports indicate that the patient became septic?
   a. If so, please provide FDA's findings in each case, in full detail, and provide documentation as described in item #1, *supra*.
   b. If FDA has not investigated any non-fatal sepsis cases, please explain why FDA has not done so.

5. Has FDA investigated, examined, or studied the life-threatening RU-486 adverse events (*e.g.*, hemorrhage and ectopic pregnancies) other than those related to septic shock resulting in death?
   a. If so, please summarize FDA's findings in each case, in full detail, and provide documentation as described in item #1, *supra*.
   b. If no findings were made, please explain why FDA has not done so.

6. Has FDA or CDC investigated, examined, or studied the deaths of women in States other than California that were "pregnancy related" and may have been caused by RU-486 abortions?
    a. If so, were any of those deaths related to *Clostridium sordellii*?
    b. If there has been no investigation, please explain why FDA has not done so.

7. Has FDA or CDC examined Medicaid payment records from States other than California to look for admissions for infections that may be associated with RU-486 abortions?
    a. If so, please summarize FDA's findings in each case, in full detail, and provide documentation as described in item #1, *supra*.
    b. If there has been no examination of such payment records, please explain why FDA has not done so.

8. It has been suggested that the infections may be related to the off-label use of the vaginal administration of misoprostol. Has FDA investigated, examined, or studied this possibility?
    a. If so, please explain why the vaginal use of misoprostol in other obstetrical and gynecological settings has not produced infections from *C. sordelli*.

9. Danco Laboratories, the manufacturer of RU-486, waited until November 2004 to mention risk of bacterial infection on the drug's warning label. Did the FDA work with Danco on this label change?
    a. If so, why did it take so long to make a label change informing the public of these risks – even after these risks had caused deaths?

10. An examination of over 800 RU-486 regimen adverse event reports reveals a high number of serious and life-threatening bleeding cases. Has FDA/CDC explored the possibility that these adverse events could be caused by *Clostridium sordellii* hemorrhagic toxins or hemorrhagic toxins from other bacterial species? If so, provide details of what has been learned.

11. Professor R.P. Miech, in a recent article on RU-486 and septic shock related to *C. sordellii* infections,[9] references, at fn. 26, a 1992 article by Lazar and others that studied the effect of RU-486's antiglucocorticoid properties on the development of septic shock in mice.[10]
    a. Was this article submitted to the FDA during any phase of the mifepristone drug testing and approval process?
    b. Did the FDA staff review the article during any phase of the RU-486 drug approval process?

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[9] R. P. Miech, *Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii*, 39 Annals of Pharamcotherapy 1483 (2005).

[10] G. Lazar, *et al.*, *Modification of septic shock in mice by the antiglucocorticoid RU 38486*, 36 Circulatory Shock 180 (1992) (Blocking glucocorticoid receptors with a single dose of mifepristone considerably lowered the survival rate of experimental mice.).

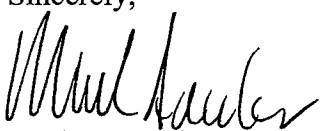
c. Did the FDA ask the drug sponsor to conduct studies looking at IL-10 production in normal non-pregnant human females receiving RU-486?
d. If the article was not received by the FDA, or received but not reviewed, please explain why that occurred.

12. Based on the findings of Lazar and others, *see question #12,* the laboratory observation of RU-486 lethality during sepsis in mammals was established. Did the New Drug Application sponsor provide FDA with any further data from animal studies to elucidate the nature of this lethal effect or to quantify how often it might occur in higher mammals when septic? (Such data could have been used to extrapolate the risk to humans.)

13. Subcommittee staff is aware that an Ohio abortion clinic director told a federal district court in litigation challenging Ohio's medical abortion statute that his clinic does not use the FDA-approved Patient Agreement form.
    a. Has FDA heard of similar statements about clinics in Ohio or any other State?
    b. How often does FDA audit Patient Agreement forms for Subpart H drugs or drugs subject to an approved risk management program in general?
    c. How often has FDA conducted audits to verify that only FDA-approved Patient and Prescriber Agreement forms are being used by RU-486 providers?
    d. Can an RU-486 provider offer alternate or ancillary patient agreement forms without obtaining prior approval of those forms from FDA?
    e. Could a provider comply with informed consent requirements if he/she used an alternate, unapproved form? If he/she used no form?
    f. What due diligence requirements has FDA placed on Danco to ensure that Danco's providers comply with the approved risk management program?

In light of the fatalities and risks surrounding RU-486, and the paramount importance of women's health, I wish to proceed quickly with this investigation in preparation for an oversight hearing. Therefore, your responses to these questions should be submitted separately as completed, and no later than 12:00pm, Monday, February 6, 2006 for all responses. Please also consider who the appropriate Administration witnesses may be for the oversight hearing into this serious matter.

Sincerely,



Mark E. Souder
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Government Reform Committee

Attachment: Definitions

CC: Julie Gerberding, M.D., Director, Centers for Disease Control and Prevention

ATTACHMENT

1. The term "documents" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "related to" or "relating to" means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.